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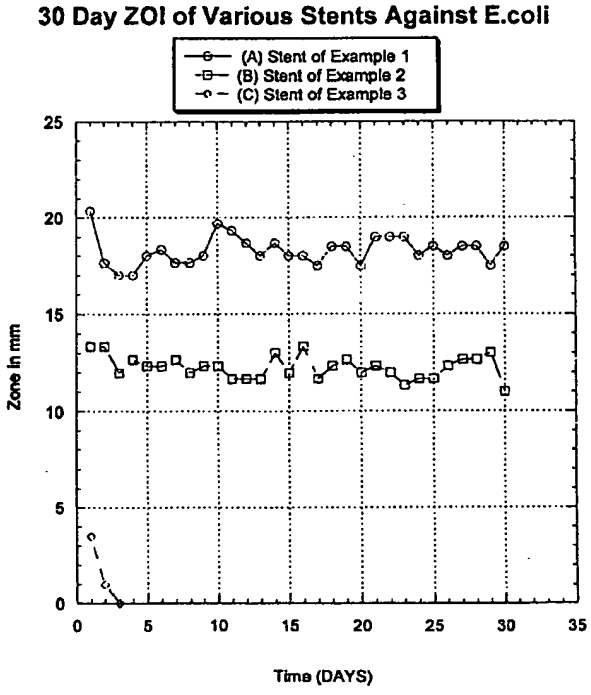
(54) Title: LUBRICIOUS MEDICAL DEVICES

(57) Abstract

Lubricious medical devices having physiologically active ingredients imbibed therein disclosed. A variety of polymeric substrates such as, for example, catheters, stents, dilatation balloons, guide wires, endotracheal tubes, instruments, implants and other medical devices can provide lubricity and abrasion resistance as well as substantially constant release profiles of the physiologically active ingredients for extended periods, e.g., 3 to 30 days or more.



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Description

LUBRICIOUS MEDICAL DEVICES

Field of the Invention

The present invention relates to lubricious medical devices. More specifically, the present invention relates to lubricious medical devices having a physiologically active ingredient imbibed therein.

Background of the Invention

A variety of lubricious coatings have been proposed for use on medical devices such as, for example, catheters, guide wires, endotracheal tubes and implants. Common materials used in the art to provide lubricious coatings for medical devices include, for example, oil, silicone and polymeric materials, such as polyN-vinylpyrrolidone, hydrophilic polyurethanes, Teflon, polyethylene oxide and polyacrylic acid. Among the most common materials used to provide lubricious coatings are hydrophilic polymers which are covalently bonded to the substrate with a binder polymer having reactive functional groups, e.g., isocyanate, aldehyde and epoxy groups. Other binder polymers comprise, for example, copolymers containing a vinyl moiety, such as vinyl chloride or vinyl acetate, and a carboxylic acid moiety. Details of such coatings are disclosed, for example, in U.S. Patent Nos. 5,091,205 issued February 25, 1992 and 5,731,087 issued March 24, 1998.

Often it is desirable to deliver a physiologically active ingredient from the medical device to a patient while it is in contact with the patient's body. As used herein, the term "physiologically active ingredient" means any compound or

element that has a therapeutic, medicinal or diagnostic effect on a human or animal. Typical physiologically active ingredients include, for example, drugs and antimicrobial agents.

Although the delivery of physiologically active ingredients from medical devices such as catheters or stents has generated a great deal of interest in the scientific and medical community, the effectiveness of such methods has heretofore been generally unsatisfactory. One of the reasons suspected for the unsatisfactory performance of such medical devices is that only a limited amount of the physiologically active ingredient can typically be incorporated into the coatings on the medical devices while still retaining the desired lubricity characteristics. As a result, the delivery of the physiologically active ingredient is often insufficient to provide a therapeutic dose in the case of a drug, or exceed the minimum inhibitory concentration ("MIC") to annihilate the intended microorganisms. Also, incorporation of physiologically active ingredients into the coatings of such medical devices often fails to provide a sustained and useful release profile rate which is sufficient to enable the medical device to remain in contact with the body for an extended length of time, e.g., 3 to 30 days or longer. This problem is especially acute with physiologically active ingredients which have low water solubility. On the other hand, if attempts are made to incorporate large amounts of physiologically active ingredients into the coatings of lubricious medical devices, the high level of incorporation can adversely affect the lubricity of the coating or the physiologically active ingredient may be released from the coating after insertion into the body of the patient at a release rate which is higher than a safe dosage for the patient.

Accordingly, improved lubricious medical devices are desired which have an effective amount of a physiologically active ingredient incorporated therein and which can release the physiologically active ingredient at a substantially constant release rate for an extended period of time, e.g. from about 3 to 30 days or longer, and provide a patient with a desired dosage of the physiologically active ingredient.

Summary of the Invention

In accordance with the present invention, improved lubricious medical devices such as, for example, catheters, guide wires, endotrachael tubes, balloons and implants are provided. The lubricious medical devices of the present invention comprise a polymeric substrate which has imbibed therein a physiologically active ingredient in an amount effective to provide a substantially constant release rate of the physiologically active ingredient at a dosage effective to accomplish the desired effect.

By the present invention it is now possible to provide desired dosages of physiologically active ingredients, especially those having low water solubility, in a controlled manner without detracting from the lubricity characteristics of the medical device.

The present invention also provides methods for the delivery of physiologically active ingredients to patients using the lubricious medical devices of the present invention as well as processes for making the lubricious medical devices.

Detailed Description of the Invention

Typical physiologically active ingredients suitable for use in accordance with the present invention include, for example, drugs and antimicrobial agents.

Examples of drug classes which may be utilized in accordance with the present invention include abortifacients, hypnotics, sedatives, tranquilizers, anti-inflammatory agents, antihistamines, anti-tussives, anti-convulsants, muscle relaxants, anti-tumor agents; for example those of the treatment of malignant neoplasia, local anaesthetics, anti-parkinson agents, diuretics, for example those containing potassium, such as potassium iodide preparations, for example those of the treatment of mental illness, for example preparations containing lithium for use in the treatment of manic depression, anti-spasmodics, anti-ulcer agents, cardiovascular agents, preparations containing hormones, for example androgenic estrongeic and progestational hormones, notably steroids such as oestradiol, sympathiomimetic agents, hypoglycaemic agents, nutritional agents, preparations containing enzymes of various types of activity, for example chymotrypsin, preparations containing analgesics, for example aspirin, and agents with other types of actions including nematocides, agents of veterinary application, contraceptives, e.g., spermicides, virucides, vitamins, vasodilators, antacids, kerolytic agents, anti-diarrhea agents, anti-alopecia agents, wound healing agents, and the like.

Specific examples of drugs which may be suitable for use in accordance with the present invention, depending on their water solubility, include ibuprofen, ketoprofen, chlorthalidone, sulphadimadine, papaverine, sulphamethoxydiazine,

hydrochlorothiazide, bendrofluazide, acetohexamide, diazepam, glipizide, nifedipine, griseofulvin, paracetamol, indomethacin, chlorpropamide, phenoxybenzamine , sulfathiazole, nitrazepam, furosemide, phenytoin, hydroflumethazide, tolbutamide, thialkylperazine maleate, dizoxin, reserpine, acetazolamide, methazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, acetaminophen, salicylic acid, methotrexate, acetyl sulfisoxazole, erythromycin, progestins, estroginie, progestational, corticosteroids, and the like. These drugs cover a wide range of solubilities in water. The present invention is particularly effective for those drugs which have a low degree of water solubility. The water solubility of drugs can be readily identified in medical references such as The Merck Index.

Often, the physiologically active ingredients, e.g., drugs or antimicrobial agents, suitable for use in accordance with the present invention, will be substantially water-insoluble, i.e., have a water solubility of less than about 2000 parts per million by weight ("ppmw"), preferably less than about 1000 ppmw and more preferably less than about 600 ppmw. As used herein, the term "water-solubility" means the amount of material, e.g., the physiologically active ingredient, which is soluble in distilled water (pH = 7.0) at 20°C and one atmosphere unless otherwise stated. For instance, 2,4,4'-trichloro-2'-hydroxydiphenyl ether has a water solubility of 10 ppm at 20°C, 8-hydroxyquinoline has a water solubility of 520 ppm at 18°C, Eiythromycin has a water solubility of 2100 ppm, Rifampin has water solubility of 2500 ppm, and Minocycline has a water solubility of 52,000 ppm. All measured in neutral water.

A typical antimicrobial agent suitable for use in accordance with the present invention is one derived from a halogenated 2-hydroxy-diphenyl ether or a halogenated 2-acyloxy-diphenyl ether such as, for example, 2,4,4'-trichloro-2'-hydroxy diphenyl ether.

Typical microorganisms include bacteria such as staphylococcus epidermis, staphylococcus aureus, Escherichia coli and Protens mirabilis, fungi and yeast such as Aspergillus fumigatus and Candia albicaus.

Antimicrobial agents which may be useful for treating microorganisms according to this invention, depending on their water solubility, include, for example, the biguanides, especially chlorhexidine and its salts, including chlorhexidine acetate, chlorhexidine gluconate, chlorhexidine hydrochloride, and chlorhexidine sulfate, silver and its salts, including silver acetate, silver benzoate, silver carbonate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine, polymyxin, tetracycline, aminoglycosides, such as tobramycin and gentamicin, rifampicin, bacitracin, neomycin, chloramphenicol, miconazole, quinolones such as oxolinic acid, norfloxaci, nalidixic acid, pefloxacin, enoxacin and ciprofloxacin, penicillins such as oxacillin and pipracil, nonoxynol 9, fusidic acid, cephalosporins, and combinations thereof.

The lubricious polymers suitable for use in accordance with the present invention comprise any polymers which are substantially more lubricious when wetted with an aqueous liquid than when dried, e.g., as evidenced by a reduction in the coefficient of friction. Typically, the lubricious polymers have a water solubility of at least about 1.0 wt. % and preferably at least

about 2.0 wt. % or are water-swellable. As used herein, the term "water-swellable" means a substantially hydrophilic polymer which, even though is not soluble in water, would absorb sufficient water to render it lubricious in the hydrated state. In addition, the term "hydrophilic" as used herein means that water droplets do not readily form beads on the surface of such hydrophilic material, but instead, the water droplets tend to assume a contact angle of less than 45° and readily spread on its surface.

Preferred hydrophilic polymers include, but are not limited to, those selected from the group consisting of polyvinyl compounds, polysaccharides, polyurethanes, polyacrylates, polyacrylamides, polyalkylene oxides, and copolymers, complexes, mixtures, and derivatives thereof. PolyN-vinyl lactams are preferred polyvinyl compounds for use in accordance with the present invention. The term "polyN-vinyl lactam" as used herein means homopolymers and copolymers of such N-vinyl lactams as N-vinyl pyrrolidone, N-vinyl butyrolactam, N-vinyl caprolactam, and the like, as well as the foregoing prepared with minor amounts, for example, up to about 20 weight percent, of one or a mixture of other vinyl monomers copolymerizable with the N-vinyl lactams. Of the polyN-vinyl lactams, the polyN-vinyl pyrrolidone homopolymers are preferred. A variety of polyN-vinyl pyrrolidones are commercially available and of these a polyN-vinyl pyrrolidone having a K-value of at least about 30 is especially preferred. The K valve is a measure of molecular weight, the details of which are known to those skilled in the art. Other preferred hydrophilic polymers for use in accordance with the present invention include, but are not limited to, those

selected from the group consisting of N-vinylpyrrolidone-hydroxyethyl acrylate copolymers, carboxymethyl cellulose, hydroxyethyl cellulose, polyacrylamide, polyhydroxyethyl-acrylate, cationically-modified hydroxyethyl cellulose, polyacrylic acid, polyethylene oxides, and complexes, mixtures , and derivatives thereof. Especially preferred are polyN-vinylpyrrolidone, polyacrylic acid polyethylene oxide and cellulosics, such as, for example, carboxymethyl cellulose and cationically modified cellulose.

The lubricious polymers suitable for use in accordance with the present invention can be nonionic, cationic, anionic or amphoteric. Typically, the molecular weight of the lubricious polymers is from about 100,000 to 2,000,000,000 grams per gram mole, preferably from about 200,000 to 5,000,000 grams per gram mole, and, more preferably, from about 300,000 to 2,000,000 grams per gram mole. As used herein, the term "molecular weight" means weight average molecular weight. Methods for determining weight average molecular weight, e.g., light scattering, are known to those skilled in the art. Further details concerning the preparation and selection of lubricious polymers suitable for use in accordance with the present invention are known to those skilled in the art. Such hydrophilic polymers are readily commercially available from a variety of sources such as, for example, Union Carbide Corporation, Danbury, Ct.

Preferably, a binder polymer having functionality to promote bonding of the lubricious polymer to the medical device substrate is used in accordance with the present invention. Typical binder polymers comprise moieties which form a covalent bond between the binder polymer and the lubricious polymer, e.g.,

isocyanate, aldehyde or epoxy moieties, or those which primarily form a hydrogen or ionic bond, e.g, polymers which comprise a vinyl moiety, such as vinyl chloride or vinyl acetate and a carboxylic acid moiety. Further details of such binder polymers are known in the art and described for example in U.S. Patent Nos. 5,091,205 issued February 25, 1992 and 5,731,087 issued March 24, 1998.

In addition to the binder polymers, lubricious polymers and physiologically active ingredients, the lubricious coatings of the present invention may comprise one or more additives normally used in coating formulations such as, for example, surfactants, preservatives, viscosity modifiers, pigments, dyes, and other additives known to those skilled in the art. Additionally, other functional additives which are ionically bonded to the hydrophilic polymer may also be used. These additives include physiologically active ingredients such as, for example, therapeutic agents, antithrombogenic agents, antimicrobial agents and antibiotic agents. When ionic additives are employed in the coating, e.g., heparin, which is anionic, it is preferred to use a cationic lubricious polymer, e.g., a cationically-modified hydroxyethyl cellulose. Similarly, when an additive is cationic, it is preferred to use an anionic lubricious polymer, e.g., a polyacrylic acid-acrylamide polymer. The combination of an additive and a lubricious polymer may be varied as needed to provide the desired performance.

The polymeric substrates to which the lubricious coatings of the present invention can be applied are not limited. The substances which are usable for the substrates include, but are not limited to, various organic polymeric compounds such as, for

example, polyamides, polyesters, e.g., polyethylene terephthalate and polystyrene terephthalate, polyvinyl chloride, polyvinylidene chloride, polystyrene, polyacrylic esters, polymethylmethacrylate and other polymethacrylic esters, polyacrylonitrile, polyethylene, polypropylene, polyurethane, polyvinyl acetate, silicone resins, polycarbonate, polysulfone, polybutadiene-styrene copolymers, polyisoprene, nylon, polyethylene, polypropylene, polybutylene, halogenated polyolefins, various latexes, various copolymers, various derivatives and blends thereof. The polymer substrates may also comprise, in addition to the substrate polymer, various inorganic and metallic substances such as, for example, glass, ceramics, stainless steel, and a super elastic metal or shape memory alloys such as Ni-Ti alloy, for example. Typical medical devices to which the lubricious coatings of the present invention can be applied include, but are not limited to, catheters, balloon catheters, guide wires, endotracheal tubes, implants and other medical devices.

The lubricious coatings of the present invention may be applied by either a two-step coating process or a one-step coating process. In a preferred two-step coating process, the portion of the substrate to be coated is first coated with the binder polymer and subsequently coated with the lubricious polymer. In a preferred one-step coating process, the binder polymer and lubricious polymer are applied to the substrate in a single step. Any conventional liquid coating processes may be utilized in accordance with the present invention. Such processes include, for example, dip-coating, spray-coating, knife-coating and roller coating. Dip-coating is a preferred coating method in accordance with the present invention.

In preferred coating processes of the present invention, the binder polymers and the lubricious polymers may be delivered from liquids contained in either a solution, a dispersion or an emulsion of the polymers. In the one-step coating methods, the binder polymers and the lubricious polymers are contained in the same liquid medium. In the two-step methods, the binder polymers and the lubricious polymers are contained in separate liquid mediums. Additional coating steps may also be employed to introduce different polymers or additives, e.g., the physiologically active ingredient as hereinafter described. The liquid mediums used for delivering the binder polymers and lubricious polymers may be organic, aqueous or an organic-aqueous mixture. The liquid medium used for delivering the binder polymer can be selected so that it has some solvency for the substrate, i.e., when the substrate is polymeric. This can enhance the adhesion between the binder polymer and the substrate and aid to the film formation of the coating material. Preferred liquid mediums for delivering the binder polymers and lubricious polymers include, but are not limited to, esters, e.g., ethyl acetate, isopropyl acetate, ethyl lactate; alcohols, e.g., isopropyl alcohol, ethanol, butanol; ketones, e.g., acetone, methylethylketone, diacetone alcohol, methyl isobutyl ketone; amides such as dimethyl formamide; toluene; glycol ethers such as butyl glycol ether; chlorinated solvents such as dichloroethane, water, and mixtures thereof. Preferably, the liquid mediums are selected so that the binder polymers and lubricious polymer evenly wet the surface of the substrate to be coated.

Preferably, the concentration of the binder polymer and the lubricious polymers in the liquid mediums are sufficient to

provide the desired amounts of the respective polymers in the lubricious coatings. Typically, the concentration of the binder polymers in the liquid medium will range from about 0.05 to 10 weight percent and, preferably, from about 0.2 to 2 weight percent based on the total weight of the liquid medium. Typically, the concentration of the lubricious polymers will range from about 0.1 to 20 weight percent and, preferably, from about 0.5 to 5 weight percent, based upon the total weight of the liquid medium. Further details concerning the selection of liquid mediums for delivering the binder polymers and lubricious polymers of the present invention are known to those skilled in the art.

The coating processes of the present invention are preferably conducted in a liquid phase at atmospheric pressure and at a temperature from about 20 to 90°C. The residence times for contacting the surface of the substrate to be coated with the liquid mediums containing the binder polymer or the lubricious polymer, or both, range from about 1 second to 30 minutes, preferably from about 5 seconds to 10 minutes. It is generally desirable to dry the coatings after application of the coating at a temperature from about 30 to 150°C, preferably in a forced-air oven. Microwave ovens, vacuum ovens and infrared heaters may also be used if desired. Typical drying times range from about 1 minute to 24 hours and preferably range from about 10 minutes to 10 hours. When a two-step coating process is employed, it is preferred to dry the binder polymer before application of the lubricious polymer.

The lubricious coatings which result from the coating processes of the present invention typically have a thickness of

from about 0.05 to 10 microns, and preferably from about 0.1 to about 5 microns. When a two-step coating process is employed, the resulting coating preferably comprises an inner layer which is rich, i.e., greater than 50%, in the binder polymer which contacts the surface of the substrate, and an outer layer which is rich, i.e., greater than 50%, in the lubricious polymer which contacts the inner layer. The outer layer, which is rich in the lubricious polymer, has an outer surface which becomes lubricious when exposed to an aqueous or organic liquid. When a one-step coating process is employed, the resulting coating comprises a single layer which is preferably a substantially homogeneous mixture of the binder polymer and the lubricious polymer. However, since the binder polymer will often have more affinity for the substrate than the lubricious polymer, it is believed that there may be a higher concentration of the binder polymer within or near the surface of the substrate.

In order to imbibe the physiologically active ingredient into the medical device in accordance with the processes of the present invention, a polymeric substrate having a matrix with (i) an internal region comprising a substrate polymer (as described above) and (ii) an outer surface is contacted with a liquid medium (as described above) having solvency for the substrate polymer. As used herein, the term "solvency" means that the liquid medium is a solvent for the substrate polymer (at the coating temperature) or is effective to promote swelling of the substrate polymer. The contacting can be conducted prior to, simultaneously with or after the application of the lubricious polymer to the polymeric substrate. Preferably, the contacting with the liquid medium comprising the physiologically active

ingredient is conducted prior to the application of the lubricious polymer. As used herein the term "imbibing" means to cause the transport of the physiologically active ingredient from the liquid medium to the internal region of the matrix of the substrate polymer.

The liquid medium comprises an effective concentration of the physiologically active ingredient to promote the imbibing of the physiologically active ingredient into the matrix of the substrate polymer.

The imbibing process is typically carried out at atmospheric pressure, and at a temperature of from about 20 to 90°C by dipping, spraying, rolling or otherwise contacting the polymeric substrate in the liquid medium for a relatively short duration such that there is preferably no more than a 10% change, more preferably no more than a 7% change in either the longitudinal or horizontal dimension or shape upon drying of the polymeric substrate. Preferably, the cross-sectional dimension, e.g., diameter of a catheter, evidences no more than a 10% change in the cross-sectional dimension after contacting with the liquid medium as compared to the cross-sectional dimension prior to said contacting. The resulting imbibed substrate can be dried as described above either before or after applying the lubricious coating.

Quite surprisingly, in accordance with the present invention, it has been found that relatively short contacting times coupled with relatively high concentrations of the physiologically active ingredient can result in substantially less dimensional change than longer contacting times with lower concentrations of the physiologically active ingredient. Typically, in accordance

with the present invention, the contacting time has a duration of from about 5 sec. to 60 minutes, preferably from about 30 sec. to 30 minutes and more preferably from about 1 to 20 minutes. Typically the liquid medium will contain from about 5 to 50 wt. %, preferably from about 7.5 to 40 wt. %, more preferably from about 8 to 25 wt. % and most preferably from about 10 to 20 wt. % of the physiologically active ingredient based on the total weight of the liquid medium.

In addition, in accordance with the present invention, more than one liquid medium can be used to effect the imbibing. For instance, one liquid medium may be a solvent for the physiologically active ingredient and a solvent or swelling agent for the polymeric substrate. Another liquid medium may be a solvent for the physiologically active ingredient and a non-solvent for the polymeric substrate. The various liquid mediums can be combined in a manner such that the resulting mixture, while capable of imbibing the physiologically active ingredient into the polymeric substrate, causes minimal dimensional changes to the polymeric substrate.

Quite surprisingly, in accordance with the present invention, it has been found that the release rates of the physiologically active ingredients described in this invention can be predicted using the following equation:

$$dm/dt = K C_L \qquad \text{(Equation 1)}$$

where dm/dt is the release rate of the physiologically active ingredient, K is a constant to be measured experimentally, and C_L is the loading of the physiologically active ingredient in the

device. For example, when the medical device is a polymeric stent made of (ethylene-vinyl acetate) copolymer coated with a lubricious coating and the physiologically active ingredient is Irgasan DP 300, 2,4,4'-trichloro-2'-hydroxyphenyl ether, K has been measured experimentally to be 4.47×10^{-5} hr^{-1}. Once this constant has been determined experimentally, the Equation 1 becomes useful for the design of any desired release rate of Irgasan DP 300 such that the release dosage would be both therapeutically effective for the patient or animal and safe. Table 1 illustrates the correlation between the Irgasan DP 300 release rate and Irgasan DP 300 loading for this particular polymeric medical device.

TABLE 1

Irgasan Loading (milligrams per 100 milligrams of Stent)	Irgasan Release Rate (micrograms per 100 milligrams of Stent)
0	0
0.2	0.2
1.8	1.7
5.3	6.6

The total amount of the physiologically active ingredient imbibed into the matrix is effective to provide a substantially constant release rate of the physiologically active ingredient when the lubricious medical device is contacted with a physiologically saline solution, i.e., 9 grams of sodium chloride per liter of water, for at least 3 days, preferably at least 7 days. As used herein, the term "substantially constant release rate" means that the release rate of the physiologically active ingredient after 3 days is at least 50%, preferably at least 60%, of the release rate after 1 day. In cases where the physiologically active ingredient is an antimicrobial, it is preferred that the release rate after 3 days is higher than the MIC for the microorganism. Preferably, the zone of inhibition ("ZOI") will be at least 5 millimeters, preferably at least 10 millimeters, after 3 days. Typically, the matrix comprises at least 5 wt. %, preferably at least 10 wt. % of the physiologically active ingredient.

In one aspect of the present invention, a portion of the physiologically active ingredient is comprised in the lubricious coating layer. In this aspect of the invention, typically less than

about 50 wt. %, preferably less than about 20 wt. %, of the total amount of the physiologically active ingredient comprised in the lubricious medical device is comprised in the lubricious polymer layer.

The following examples are presented for illustrative purposes and are not intended to limit the scope of the claims which follow.

Examples

The following test was employed in conducting the examples.

Coefficient of Friction Test : A physiologically active ingredientr of catheters is laid parallel to each other on a horizontal stainless steel platform at a distance of about 1.5 inches apart. The platform and the catheters are subsequently wetted thoroughly with about 100 milliliters ("ml") of distilled water. A rectangular shaped aluminum block (2x2x3 inches) weighing 100 grams ("g") wrapped in a wet cellulose acetate membrane is placed on top of the catheters at the free-moving end of the platform. Thereafter, the platform is raised gradually and steadily from the free-moving end until an inclination angle "Ø" is reached where the block begins to slide on the wet catheter surfaces. The coefficient of friction ("COF") is calculated as tangent Ø.

The following examples are provided for illustrative purposes and are not intended to limit the scope of the claims which follow.

EXAMPLE 1

This example illustrates the incorporation of a physiologically active ingredient (also referred to herein as " physiologically active ingredient "), i.e., an antimicrobial, Irgasan DP 300, into a polymeric device before the coating process. 8 French size stents extruded from (ethylene-vinyl acetate)copolymer were cut into 10 inch long pieces. The stents were cleaned with isopropyl alcohol(IPA) and air dried. The stents were then dipped into a toluene solution containing 15% by weight of Irgasan DP 300 for a period of 10 min., and followed by drying in a forced air oven at 65°C for 3 hrs. Thereafter, stents were removed from the oven and dipped in another coating bath containing 3.3% by weight of poly(vinyl pyrrolidone)(PVP, Kollidon® 90F produced by BASF of Germany), 3.3% of UCAR® Solution Vinyl Resin VMCA(a (vinyl chloride-vinyl acetate-maleic anhydride)copolymer produced by Union Carbide of Danbury, CT), and 46.7% each of acetone and ethyl lactate for a period of 30 seconds, and followed by drying for another 3 hrs under the same condition as described above. The finished coating had a contact angle with water of less than 5°. Lubricity measurement in the presence of distilled water with a Sliding-Block Tester showed a coefficient of friction(COF) of 0.13 as compared to that of 1.73 for the uncoated stent.

EXAMPLE 2

This example illustrates the loading of Irgasan DP 300 during the coating process according to the method of this invention. The same stents used in Example 1 were cleaned and

air dried. The stents were dipped in a solution of POLYSLIP® COATING P-106(an aromatic polyisocyanate in toluene produced by Union Carbide of Danbury, CT) containing 15% by weight of Irgasan DP 300 for 1 min. and followed by drying in a forced-air oven at 65°C for 20 min. The stents were then removed from the oven and dipped in another coating bath containing POLYSLIP COATING T-503M(a dispersion of poly(acrylic acid) in a solvent mixture of dimethyl formamide, t-butyl alcohol, and methyl ethyl ketone produced by Union Carbide of Danbury, CT) for 1 second and followed by drying at 65°C for 1 hr. The coated stents were further dipped in an aqueous sodium phosphate bath for 1 second and followed by drying at 65°C for 12 hrs. The finished coating is smooth and uniform. Lubricity measurement in water showed a COF of 0.13 as compared to that of 1.73 for the uncoated stent.

EXAMPLE 3

Control this example illustrates the loading of Irgasan DP 300 during the coating process, but not following the method of this invention. The same stents used in Example 1 were cleaned with IPA and air dried. The stents were dipped in a bath containing POLYSLIP COATING p-106 for 30 seconds and followed by drying in a forced-air oven at 65°C for 30 min. The stents were then removed from the oven, and dipped in another coating bath containing POLYLSIP COATING T-503M and 3.5% by weight of Irgasan DP 300 for a period of 1 second, and followed by drying at 65°C for 1 hr. The stents were then dipped in an aqueous sodium phosphate solution for 1 second, and followed by drying for 12 hrs. at 65°C. The finished coating was smooth and

uniform, and showed a contact angle with water of 32°. Lubricity measurement in water showed a COF of 0.11 as compared to that of 1.73 for the uncoated stent.

EXAMPLE 4

The release rates of Irgasan DP 300 from the stents prepared according to Examples 1-3 in phosphated buffered saline("PBS") at body temperature were measured for a seven-day duration using a high pressure liquid chromatography ("HPLC") methodology disclosed in "Irgasan DP 300 Broad Spectrum Antimicrobial" published by Ciba Geigy Corporation, Greensboro, North Carolina (1988). For each series of experiment, 4 pieces of 8 cm length stents were used. Two were used for measuring the initial total Irgasan DP 300 loading, and the other for measuring the Irgasan release rate in PBS for a consecutive seven day duration. Each 8 cm stent was cut into 4 pieces and placed in a sealed glass vial containing 5 ml of PBS. The glass vial is placed in a culture chamber at 37°C for a 24 hr duration. At the end of the 24 hr period, the aqueous extract in the vial was removed for Irgasan DP 300 determination. The extracted stents were transferred to a new vial with 5 ml of fresh PBS solution, and placed in the culture chamber for another 24 hrs. This procedure was repeated for a total of seven times. Thus, the release rate of Irgasan DP 300 from the same 8 cm stent was measured for 7 consecutive days. At the end of the seventh day, the residual total Irgasan DP 300 in the stent was measured. For total Irgasan DP 300 measurement, the extraction was done using 15 ml of methyl ethyl ketone and the HPLC methodology was

otherwise similar to that used for the PBS extract. The HPLC results are complied in Table 2.

Table 2
Irgasan DP 300 Release Rates From Different Stents

Stent	Example 1A	Example ** 1B	Example 2A	Example 2B	Example 3A	Example 3B
Initial total Irgasan DP300 (milligram per centimeter of length) mg/cm	2.49	2.60	0.77	0.82	0.05	0.04
Irgasan DP300 Release Rate 1st day, (microgram per centimeter of length per 24 hours) ug/cm stent*	3.62	2.75	0.73	0.87	0.05	0.03

Table 2 con't..
Irgasan DP 300 Release Rates From Different Stents

2nd day	5.19	2.99	0.62	0.70	0.07	0.05
3rd day	4.53	3.60	0.65	0.67	0.05	0.02
4th day	3.38	3.31	0.51	0.52	0.03	0.03
5th day	3.41	2.56	0.51	0.67	0.04	0.07
6th day	3.61	2.36	0.70	0.51	0.02	0.03
7th day	2.42	3.21	0.77	0.63	0.03	0.03
Residual total Irgasan DP300 mg/cm	2.33	2.57	0.76	0.75	0.06	0.05

*1 ug/cm stent = 1.6 ug/ml or 1.6 ppm in this series of experiments
**A and B denote duplicate samples

The release rates of Irgasan DP 300 from Samples 1A, 1B, 2A. 2B, 3A, and 3B were maintained at substantially constant rates. During the seven days duration when the release rates were followed, none dropped below 50% of its initial release rate.

According to Ciba Specialty Chemicals' methodology, the minimum-inhibitory-concentration(MIC) of Irgasan DP 300 against two common infectious bacteria, Staphylococcus aureus and Escherichia coli, are from 0.01 to 0.1ppm and from 0.03 to 0.3 ppm, respectively. On the basis of the release rate data for Irgasan DP 300 listed in Table 1, one would expect the stents prepared in Example 1 and 2 should be effective in controlling the growth of both of the two infectious bacteria. On the other hand, the marginal release rate of Irgasan DP 300 from Samples 3A and 3B prepared in Example 3 may show only marginal bioefficacy against S. aureus and very little against E. coli. This will be demonstrated by the bioefficacy results shown in the next series of experiments.

EXAMPLE 5

The bioefficacy of the stents prepared in Examples 1-3 were determined by the zone-of-inhibition(ZOI) measurement. All ZOI tests were done in triplicates. The sterilized stents were cut to 2 cm length and placed horizontally onto an inoculated petri dish containing Trypticase and 10^6 CFU of either E. coli(ATCC 8739) or S.aureus(ATCC 6538). The petri dish was placed in a 37°C culture chamber for 24 hrs. At the end of 24 hrs, the petri dish was removed from the culture chamber and the size of the zone in mm was measured with a ruler. Thereafter, the sections of stents

were transferred to a freshly prepared inoculated petri dish containing Trypticase and 10^6 CFU of the same bacteria and placed in the culture chamber for another 24 hrs. This procedure was repeated for a total of seven times to generate seven consecutive days of ZOI data for each of the stents tested. The ZOI results are summarized in Tables 3 and 4.

Table 3

ZOI Data of Various Stents Against E. Coli(ATCC 8739)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Example 1	20.3	17.7	17	17	18	18.3	17.7
Example 2	13.3	13.3	12	12.7	12.3	12.3	12.7
Example 3	3.5	1.0	0				
Uncoated Control	0	0	0	0	0	0	0

Table 4

ZOI Data of Various Stents Against S. aureus(ATCC 6538)

Stent	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Example 1	40.0	38.0	37.7	38.3	39.7	41.0	37.3
Example 2	31.7	31.7	33.0	27.7	32.0	31.7	31.7
Example 3	11.0	11.5	12.5	12.0	11.5	11.5	11.5
Uncoated Stent	0	0	0	0	0	0	0

The bioefficacy shown in Table 4 have confirmed the prediction based on the release rate date of Irgasan DP 300 generated in Example 4. The stents prepared according to the methods of this invention from Example 1 and 2 both showed an Irgasan DP 300 release rate higher than the MIC for either of the two infectious bacteria and sustained at a substantially constant rate during the seven days of testing. They both also showed good and sustained bioefficacy against both of the two infectious bacteria. On the other hand, stents prepared according to Example 3 showed inadequate release of Irgasan DP 300 at a concentration below the MIC required for controlling E. coli. This was reflected in its poor ZOI data against this bacterium.

EXAMPLE 6

The ZOI measurement against E. coli of stents prepared in Examples 1-3 were extended for a thirty day period, and the results are plotted in Figure 1. These results show convincingly that when a stent was loaded according to the method of the present invention, as demonstrated by the stents prepared according to Example 1 and 2, it exhibited a good bioefficacy against E. coli for a sustained period of time. On the other hand, when a stent was loaded not according to the method of this invention, as demonstrated by the stents prepared according to Example 3, its bioefficacy was inferior.

EXAMPLE 7

This example illustrates a key advantage of the present invention by comparing the release rate profiles of devices

prepared according to the present invention to those of teachings described by Darouiche et al. (U.S. Patent 5,902,283, May 11, 1999) and by Solomon et al. (J. Controlled Release, 6, 343-352, 1987; U.S. Patent 4,442,133); Tridodecymethyl ammonium chloride (TDMAC) precoated catheters are commercially available from Cook Critical Care, Bloomington, Ind.). Table 5 lists the release rate profiles of minocycline and rifampin from catheters prepared according to the impregnation process described by Darouiche et al. (Example 2 and Table 5 in US Patent 5,902,283). The release rates for minocycline varied from a high of 354 on the first day to a low of 2.3 ug/cm stent/24 hrs. on the 30th day. Even on the second day, the release rate was only 15.5% of that of the first day. The release rates for Rifampin were just as irratic and vary from a high of 287 to a low of 4.5 ug/cm stent/24 hrs. The initial loading of the two antibiotics and percents remaining after given days of release are shown at the bottom portion of Table 5.

The data show that the teaching provided by Darouiche et al. did not provide a medical device which produced a sustained release of a physiologically active ingredient at a substantially constant rate for a prolonged period of time.

Table 6 lists the release rate profiles of minocycline and rifampin from catheters prepared according to the TDMAC method but were reported by Darouiche et al. (Example 2 and Table 5 in US Patent 5,902,283) The release rates of minocycline varied from a high of 23 to a low of 0.82 ug/cm stent/24 hrs. which corresponds to 16.5 and 0.59%/cm stent/24 hrs release of the initial loading of the drug, respectively. Consequently, neither of

the antibiotics produced a substantially constant release rate, which is a serious drawback from the point of view of both therapeutic effectiveness and safety to the patients.

Table 7 illustrates the effectiveness of the present invention when a substantially water-insoluble physiologically active agent, such as Irgasan DP 300 was loaded according to the method of this invention. The release rates of Irgasan 300 varied from a high of 4.09 to a low of 2.82 ug/cm stent/24 hrs which corresponds to 0.16 to 0.11%/cm stent/24 hrs. respectively. At the end of a seven-day release, there was only a 5% reduction of the Irgasan DP 300 loading in the stent from its initial value. In comparison, the Darouiche et al. catheter lost about 70-85% of its actives after only 3 days. The catheter prepared via the TDMAC method lost about 45% of its actives after only 3 days. Consequently, this example clearly demonstrates the advantage of the present invention in providing a medical device which is capable of delivering a sparingly-water-soluble drug at a substantially constant rate for a prolonged period of time.

TABLE 5

RELEASE-RATE PROFILES OF MINOCYCLINE AND RIFAMPIN REPORTED BY DAROUICHE ET AL.*

Physiologically active ingredient	Minocycline Release Rate ug/cm/24 hr	Minocycline % Release/cm/24 hr	Rifampin Release Rate ug/cm/24 hr	Rifampin % Release/cm/ 24 hr
D_0-D_1	354	52.4	287	38.6
D_1-D_2	55	8.1	24	3.2
D_2-D_3	103	15.3	213	28.6
D_3-D_{15}	9.3	1.38	4.5	0.6
D_{15}-D_{30}	2.3	0.34	5.5	0.74
Initial loading	675 ug/cm		744 ug/cm	
After 3 day release	15.3%		29.6%	
After 15 day release	7.6%		22.3 %	
After 30 day release	2.5%		11.2%	

TABLE 6

RELEASE-RATE PROFILES OF MINOCYCLINE AND RIFAMPIN USING CATHETERS TREATED BY TDMAC METHOD(derived from Example 2 and Table 5 in US Patent 5,902,283)

Physiologically active ingredient	Minocycline Release Rate ug/cm/24 hr	Minocycline % Release/cm/24 hr	Rifampin Release Rate ug/cm/24 hr	Rifampin % Release/ cm/24 hr
D_0-D_1 days	16	11.5	1.0	7.1
D_1-D-3	24	24	2.5	18.0
D_3-D_{15}	4.6	4.6	0.39	2.8
D_{15}-D_{30}	0.82	0.82	0.2	1.4
Initial loading	139 ug/cm		14 ug/cm	
After 3 day release	55.4% remaining		57.1% remaining	
After 15 day release	15.5% remaining		23.6% remaining	
After 30 day release	6.6% 6.6 ug/cm		2.1% remaining	

TABLE 7

RELEASE-RATE PROFILES OF IRGASAN DP 300 ACCORDING TO THE METHOD OF THE PRESENT INVENTION

Days	Stent A[1] Release Rate ug/cm/24 hrs	Stent A[1] % Release/cm/24 hrs	Stent B[2] Release Rate ug/cm/24 hrs	Stent B[2] % Release/cm/ 24 hrs
D_0-D1	3.19	0.10	0.80	0.10
D_1-D_2	4.09	0.16	0.66	0.08
D_2-D_3	4.07	0.16	0.66	0.08
D_3-D_4	3.35	0.13	0.52	0.07
D_4-D_5	2.99	0.12	0.59	0.07
D_5-D_6	2.99	0.12	0.61	0.08
D_6-D_7	2.82	0.11	0.70	0.09
Initial loading	2,545 ug/cm		795 ug/cm	
After 7 days	2450 ug/cm (96%) remaining		755 ug/cm (95%) remaining	

[1] Stent A prepared according to Example 1

[2] Stent B prepared according to Example 2

EXAMPLE 8

This example illustrates a preferred process for producing a lubricious coating on a polymeric medical device which contains a high loading of physiologically active agent. Example 2 was repeated with the exception that the dipping time in the POLYSLIP COATING T-503M was varied from 1 to 60 sec. As shown in the Table 8, the finished stents showed equivalent initial lubricity as measured using a Chitillon Force Gauge in the

presence of distilled water. However, the abrasion resistance of the stents increase with longer dipping time in the topcoat bath.

TABLE 8

LUBRICITY OF BIOSTATIC STENTS CONTAINING HIGH LOADING OF IRGASAN DP 300

Dipping t in topcoat bath sec	Frictional Force As is g	Frictional Force after 10 abrasions g
Control	35.5	35.5
1	3.2	27.1
30	4.3	12.3
60	2.3	2.3

EXAMPLE 9

This example demonstrates that the lubricity produced by the process of this invention for polymeric stents containing a high-loading of physiologically active agent was unaffected by the ethylene-oxide sterilization process commonly used by the medical device industry. Six French size stents extruded from (ethylene-vinyl acetate) copolymer were cut into 12 inch long pieces. The stents were cleaned with IPA and air dried. The stents were then dipped into a solution of POLYSLIP COATING P-106 containing 20% by weight of Irgasan DP 300 for 15 min. and followed by drying in a forced-air oven at 65°C for 20 min. The stents were then dipped in another coating bath containing POLYSLIP COATING T-503M for 10 sec. And followed by drying at 65°C for 2 hrs. The stents were then quenched in an aqueous sodium phosphate bath for 10 min. and followed by drying at 65°C for 11 hrs. The finished coating was uniform and smooth.

The lubricity of the stents either before or after ethylene-oxide sterilization was tested with a Chatillon Force Gauge and the results are shown in Table 9. Both the unsterilized and sterilized stents showed excellent lubricity than the uncoated controls.

TABLE 9

LUBRICITY OF STENTS CONTAINING HIGH-LOADING OF IRGASAN DP 300 BEFORE & AFTER STERILIZATION MEASURED WITH A CHATILLON FORCE GAUGE

Sample	Frictional Force As is g	Frictional Force after 20 abrasions g
Control	35.5	35.5
Unsterilized	5.8	2.5
Sterilized	0.8	0.8

EXAMPLE 10

This example illustrates the loading of Irgasan DP 300 onto stents which were already coated with a hydrophilic coating. The same stents used in Example 1 were cleaned with IPA and air dried. The stents were dipped in a coating solution identical to the PVP/UCAR Solvent Vinyl Resin VMCA solution described in Example 1 for 30 seconds, and followed by drying in a forced air oven at 65°C for 3 hrs. The stents were then removed from the oven and dipped in a toluene solution containing 3.5% by weight of Irgasan DP 300 for 30 min., and followed by drying at 65°C for 3 hrs. The finished coating was smooth and uniform. The coated stent showed a contact angle with water of 51°. The

bioefficacy of this stent was determined using the ZOI method described in Example 5, and the results are compiled in Table 10.

Table 10
ZOI Against E. Coli(ATCC 8739)
(average of triplicate measurements)

Stent	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Zone (mm)	17.3	16.3	15.7	14.7	16.7	16.0	15.7

EXAMPLE 11

This example illustrates the effects of imbibing time and concentration of the physiologically active ingredient in the imbibing solution to the loading of the physiologically active ingredient which, in turn, affects its bioefficacry performance. The same stents used in Example 1 were cleaned with IPA and air dried. The stents were then either dipped in a toluene solution containing 3.5% by weight of Irgasan DP 300 for a specified duration,or in a toluene solution containing a specific concentration of Irgasan DP 300 for a 30 min. duration, and followed by drying in a forced air over at 65°C for 3 hrs. The finished stents were uniform and smooth. The release rate of Irgasan DP 300 from these stents and their bioefficacy as measured by ZOI are listed in Table 11.

Table 11

Irgasan DP 300 Release Rate and ZOI Against E. Coli(ATCC 8739)

Sample	Imbibing Time, min.	Irgasan DP 300 Conc. Wt%	Irgasan DP 300 Release Rate,ug/ml	ZOI mm
1	10	3.5	0.52	17
2	5	3.5	0.27	13.5
3	1	3.5	0.07	8.5
4	30	1.7	27	
5	30	0.97	21	
6	30	Not determined	17	

EXAMPLE 12

This example illustrates the utility of this invention in predicting the correct release rate of a physiologically active ingredient from a polymeric device using the kinetic model represented by Equation 1. The physiologically active ingredient used in this example is Irgasan DP 300, and the polymeric devices used in this example included a variety of hydrogel coated (ethylene-vinyl acetate)copolymer stents. The total physiologically active ingredient loadings and experimental release rates of the physiologically active ingredient in PBS were measured using the HPLC method described above. The predicted release rates were calculated from the Equation 1.

Thus, there is a good agreement between the predicated release rates of Irgasan DP 300 calculated according to the kinetic model of this invention(Equation 1) and the experimental values. The results of this experiment demonstrate that a desired release rate of a physiologically active ingredient from a given polymeric device, reflecting both therapeutic effectiveness and patient safety, can be conveniently calculated from the kinetic model constructed according to the method of this invention.

Table 12

A Comparison of Predicted and Experimental Irgasan DP 300 Release Rates

Coating Type	Irgasan DP 300 Loading mg/100 mg Stent	Predicted Release Rate ug/24hr.100 mg Stent	Experimental Release Rate ug/24hr.100 mg Stent
Example 3, quenched in PVP solution	0.18	0.19	0.13
Duplicate	0.19	0.20	0.13
Example 2, quenched in 0.01 N sodium phosphate solution	1.60	1.71	1.46
Duplicate	1.63	1.75	1.76

Table 12 (continued)
A Comparison of Predicted and Experimental Irgasan DP 300 Release Rates

Coating Type	Irgasan DP 300 Loading mg/100 mg Stent	Predicted Release Rate ug/24hr.100 mg Stent	Experimental Release Rate ug/24hr.100 mg Stent
Example 2, quenched in 0.1N sodium phosphate solution	1.64	1.75	1.42
Duplicate	1.65	1.75	1.42
Example 1, except PVP/VMCA=3/1	4.12	4.41	3.91
Example 1, except PVP/VMCA=2/1	4.86	5.21	4.66
Example 1	5.48	5.88	6.29

EXAMPLE 13

This experiment illustrates the effect of imbibing time in an aggressive solvent to the dimensional integrity of the polymeric device. The same stents used in Example 1 were dipped in toluene, which is both a solvent for the Irgasan DP 300 and a swelling solvent for the polymeric device, for different durations, and followed by drying in a forced air oven at 65°C for 30 min. The dimensional changes before and after the imbibing process were measured and complied in the Table 13.

Up to 30 minutes imbibing time was used for toluene solvent without causing greater than 10% change in either diameter or length of the stent. Stents imbibed for 60 minutes or longer showed more than 12% contraction in diameter which is undesirable for the preferred aspects of this invention.

When a 50/50 isopropyl lactate/acetone mixture solvent was used for imbibing Irgasan DP 300, the dimensional stability of the ethylene-vinyl acetate polymeric stent was sufficiently good that the primary consideration for the imbibing time concerned process efficiency in loading the correct level of the physiologically active ingredient into the polymeric device.

Table 13

Dimensional Changes of (Ethylene-Vinyl Acetate)Copolymer Stents Upon Exposure To Toluene or50/50 Isopropyl Lactate/Acetone Mixture

Solvent	Imbibing Time, min.	Diameter Retention, %	Length Retention, %
Toluene	1	95.5	100
"	5	94.2	105
"	10	95.1	105.6
"	20	92.2	105.0
"	30	92.2	105.3
"	60	87.3	105.9
50/50 IL/A	1	99.7	100
"	5	99.4	100
"	10	99.0	100
"	20	98.1	100
"	30	98.1	100
"	60	97.6	100

EXAMPLE 14

This example illustrates THAT WHEN stents were imbibed with physiologically active ingredient according to the procedure of this invention, they showed good bioefficacy against E. coli. The same stents used in Example 1 were cleaned with IPA and air dried. The stents were dipped in an IPA solution containing a given concentration of Irgasan DP 300 for a given duration, and followed by drying in a forced-air oven for 30 min. The Irgasan DP 300 treated stents were then coated with a lubricious coating according to the procedure described in Example 2 with the exception that no Irgasan DP 300 was added to the POLYSLIP COATING P-106 solution. The finished coating was uniform and smooth. Bioefficacy of these stents were determined using the ZOI method described in Example 5, and the results were complied in Table 14. The stents prepared according to the process of the present invention, by imbibing Irgasan DP300 from a primer containing 15% by weight of the physiologically active ingredient for an one minute period, showed a consistent zone against E. coli for the entire test period. On the other hand, those prepared by imbibing from a primer containing 1% by weight of the physiologically active ingredient, show no detectable zone against E. coli.

EXAMPLES 15-17

Examples 15-17compares the bioefficacy performance of Foley catheters imbibed with Irgasan DP 300 using either the method of this invention. In each case, three units of 16 French Foley catheters were cleaned with IPA and air dried. The Foley catheters were dipped into a solution consisting of 1% by weight of UCAR Solution Vinyl Resin VMCA, and 49.5% each of acetone

and isopropyl lactate for 30 seconds, and followed by drying in a forced air oven at 85°C for 1 hr. The catheters were subsequently dipped in another coating bath containing a solution prepared from 1 - 10% by weight of Irgasan DP 300, 2.98% of poly(vinyl pyrrolidone), and 48.01% of each of acetone and isopropyl lactate for 1 - 10 min., and followed by drying at 85°C for 3 more hrs. The finished coating was uniform and clear. The bioefficacy of these Foley catheters against E. coli were determined by the ZOI method described in Example 5. The results of ZOI tests are shown in Table 15.

Table 14

ZOI Data Against E. Coli(ATCC 8739)

Imbibing Method	Concentration Irgasan DP 300 wt%	Imbibing Time min	ZOI mm Day 1	ZOI mm Day 2	ZOI mm: Day 3
According to the method of this invention	15	1	12	10	10
Comparative	1	30	0	0	0
Stent as is	-	-	0	0	0

Table 15

Irgasan DP 300 Imbibed Foley Catheters
ZOI Data Against E. Coli (ATCC 8739)

Sample	Conc. Of Irgasan DP 300 in solution	Imbibing Time, min.	ZOI, mm Day 1	ZOI, mm Day 4
Example 15	1%	1	16	6
Example 16	10	1	22	20
Example 17	10	10	24	20
Uncoated Stent	0	0	0	0

The Foley catheters treated according to the procedures of this invention which are exemplified by Examples 18-19 showed good bioefficacy at both day 1 and day 4. On the other hand, the Foley catheters treated by the comparative method, exemplified by Example 15, showed only marginal performance as evidenced by a marked drop in ZOI by day 4.

EXAMPLE 18-21

Examples 18-21 demonstrate the usefulness of this invention for the application to another sparingly-water-soluble physiologically active ingredient, 8-hydroxyquinoline. This physiologically active ingredient is useful as a fungistat or a disinfectant according to the Merck Index. Additionally, these examples further demonstrate the benefit of the imbibing process as described in this invention. The (ethylene-vinyl acetate) copolymer stents described in Example 1 were dipped in a toluene or IPA solution containing either 1% or 20% by weight of 8-hydroxyquinoline for an 10 sec. or 10 min. duration, and followed by drying in a forced air oven at 65°C for 30 min. The stents were then dipped in POLYSLIP COATING P-106 for 30 sec. and followed by drying in a forced air oven at 65°C for 20 min. The stents were dipped in POLYSLIP COATING T-503M solution for 1 sec., and followed by drying at 65°C for 1 hr. The stents were subsequently dipped in an aqueous sodium phosphate bath for 1 sec., and followed by drying at 65°C for 12 hrs. The finished coating is clear and smooth.

The treated stents prepared in Examples 18-21were tested for bioefficacy against E. coli using the ZOI method described in Example 5. The results are shown in Table 16.

Table 16

ZOI Data Against E. Coli (ATCC 8739)

Sample	8-HQ conc. wt% / solvent	Dipping time	Following method of this invention	ZOI, mm Day 1	ZOI, mm Day 2
Example 18	20/toluene	10 min	yes	21	16
Example 19	1/toluene	10 sec	no	0	0
Example 20	20/IPA	10 min	no	4	0
Example 21	1/IPA	10 sec	no	0	0
Uncoated Stent	-	-	-	0	0

The stents imbibed in Example 18 used a solution that contains sufficiently high concentration of the physiologically active ingredient in a solvent which is both a good solvent for the physiologically active ingredient and a good swelling solvent for the polymeric matrix for a sufficiently long duration for the physiologically active ingredient to be loaded into the device according to the criteria of this invention. The result was a effective device for controlling the growth of E. coli bacteria. On the other hand, stents prepared according to Example 19 were not effective because the concentration of the physiologically active ingredient in the solution does not permit a sufficient loading of the physiologically active ingredient to achieve bioefficacy. Example 20 and 21 show clearly the importance of selecting a suitable solvent for the imbibing process. Since IPA is not a very effective swelling solvent for the polymeric matrix, even though it is a good solvent for the physiologically active ingredient, the imbibing process was rendered ineffective regardless the concentration of the physiologically active ingredient or the imbibing time employed.

Although the invention has been described above with respect to specific aspects, those skilled in the art will recognize that other aspects are intended to be included within the scope of the claims which follow. For instance, polymers other than the specific binder polymers and lubricious polymers and physiologically active ingredients may be employed in accordance with the present invention.

Claims

It is Claimed:

1. A lubricious medical device comprising:

(a) a polymeric substrate having a matrix with; (i) an internal region comprising a substrate polymer, and (ii) an outer surface; and

(b) a layer of a lubricious polymer affixed to the outer surface, said lubricious polymer layer exhibiting a reduction in its coefficient of friction when contacted with aqueous or organic fluids;

characterized in that the matrix has imbibed therein a physiologically active ingredient, having a water solubility of less than about 2000 ppmw, which is effective to provide a substantially constant release rate of the physiologically active ingredient.

2. The lubricious medical device of claim 1 wherein the matrix comprises at least 5% by weight of a physiologically active ingredient.

3. The lubricious medical device of claim 1 having a total amount of the physiologically active ingredient which is effective to provide a substantially constant release rate of the physiologically active ingredient when the lubricious medical device is contacted with a physiological saline solution for at least 3 days.

4. The lubricious medical device of claim 3 wherein the release rate of the physiologically active ingredient after 3 days is at least 50 percent of the release rate after 1 day.

5. The lubricious medical device of claim 3 wherein the physiologically active ingredient is a therapeutic agent.

6. The lubricious medical device of claim 3 wherein the physiologically active ingredient is an antimicrobial agent for an infectious microorganism.

7. The lubricious medical device of claim 6 wherein release rate of the physiologically active ingredient after 3 days is higher than the minimum inhibitory concentration for the microorganism.

8. The lubricious medical device of claim 6 having a zone of inhibition of at least 10 millimeters after 3 days.

9. The lubricious medical device of claim 1 wherein a portion of the physiologically active ingredient is comprised in the lubricious coating layer.

10. The lubricious medical device of claim 9 wherein less than about 50 weight percent of the total amount of the physiologically active ingredient comprised in the lubricious medical device is comprised in the lubricious polymer layer.

11. The lubricious medical device of claim 1 further comprising a binder polymer having functionality to promote bonding of the lubricious polymer to the outer surface of the substrate.

12. A method for introducing a physiologically active ingredient to a human or animal, comprising contacting a lubricious medical device in accordance with claim 1 with an internal area of the human or animal for a time effective to promote the transfer of the physiologically active ingredient to the human or animal.

13. The method of claim 12 wherein said contacting is conducted for a time of from about 1 to 30 days.

14. A process for making a lubricious medical device imbibed with a physiologically active ingredient, said process comprising:

(a) contacting a polymeric substrate having a matrix with; (i) an internal region comprising a substrate polymer, and (ii) an outer surface, with a liquid medium having solvency for the substrate polymer, said liquid medium comprising an effective concentration of the physiologically active ingredient to promote the imbibing of the physiologically active ingredient into the matrix;

(b) applying a layer of a lubricious polymer to the outer surface; and

(c) removing at least a portion of the liquid medium from the polymeric substrate.

15. The process of claim 14 wherein the concentration of the physiologically active ingredient in the liquid medium is effective to provide a substantially constant release rate of the physiologically active ingredient when the lubricious medical device is contacted with a physiological saline solution for at least 3 days.

16. The process of claim 14 wherein the concentration of the physiologically active ingredient in the liquid medium is proportional to the amount of the physiologically active ingredient imbibed into the matrix.

17. The process of claim 14 wherein the medical device has a cross-sectional dimension and there is less than a 10 percent change in the cross-sectional dimension after said contacting with the liquid medium as compared to the cross-sectional dimension prior to said contacting.

18. The process of claim 17 wherein said contacting is conducted for a time of less than about 60 minutes.

19. The process of claim 17 wherein the liquid medium comprises at least about 5 weight percent of the physiologically active ingredient.

20. The process of claim 14 wherein the lubricious polymer is applied to the polymeric substrate prior to, simultaneously or after said contacting with the liquid medium.

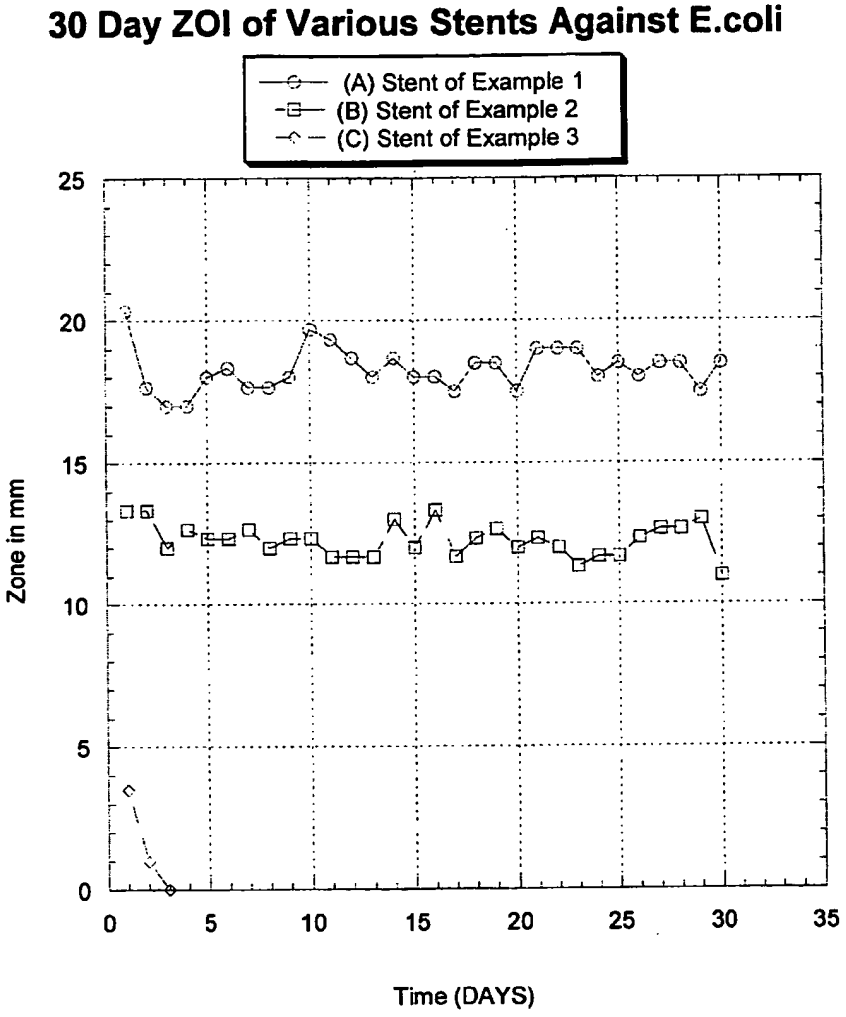
30 Day ZOI of Various Stents Against E.coli
(A) Stent of Example 1
(B) Stent of Example 2
(C) Stent of Example 3
Zone in mm
25
20
15
10
5
0
0
5
10
15
20
25
30
35
Time (DAYS)

FIGURE 1

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 00/01933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/50 A61L27/54 A61L29/14 A61L29/16 A61L31/14 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 761 243 A (UNION CARBIDE CHEM PLASTIC) 12 March 1997 (1997-03-12) page 2, line 29 - line 49 page 2, line 55 -page 3, line 55 page 4, line 35 - line 47 page 5, line 5 - line 34	1-20
X	WO 96 22114 A (VITAPHORE CORP) 25 July 1996 (1996-07-25) page 4, line 1 - line 11 page 5, line 17 - line 32 page 9, line 4 - line 38	1-7,9, 10, 12-16,20

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/US 00/01933

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 14447 A (PRISCOTT PAUL KENNETH) 24 April 1997 (1997-04-24) abstract page 4, paragraph 2 -page 5, paragraph 1 page 6, paragraph 2 -page 7, paragraph 3	1-7, 9-16,20
Y	EP 0 379 156 A (UNION CARBIDE CHEM PLASTIC) 25 July 1990 (1990-07-25) abstract page 3, line 6 - line 58 page 5, line 40 - line 58	1-7, 9-16,20

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